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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,093	DALY, JOHN	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-106* is/are pending in the application.

4a) Of the above claim(s) *1-22,29,43,59-67,69-84 and 103-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) *23-28,30-42,44-58,68 and 85-102* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/15/04, 3/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 8/23/04 and 10/7/04. Claims 1-106 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group II (claims 23-58, 68, 85-102) in the amendment filed 8/23/04 is acknowledged. Applicants' have also elected an RNA destabilizing elements in the amendment filed 8/23/04 is acknowledged. Furthermore, applicants' selection of SEQ ID NO:19 in the amendment filed 10/7/04 is acknowledged. Therefore, claims 23-28, 30-42, 44-58, 68 and 85-102 are under examination in this application.

Information Disclosure Statement

Information Disclosure Statements fled 3/15/04 and 3/26/04 have been identified and the documents considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Specification

The disclosure is objected to because of the following informalities: as the Brief Description of Drawings for figure 22 does not include a reference to figure 22A. Appropriate correction is required.

Claim Objections

Claims 44 and 45 are directed to non-elected subject matter. The claims should be amended to delete any reference to sequences other than SEQ ID NO:19.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 46, 47 and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of PEST sequences, N-terminal destabilizing amino acids, ubiquitin and biologically active fragments, variants and derivatives of these.

Applicants claim a genus of reporter proteins, selectable markers and biologically active fragments, variants or derivatives of these.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed

correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The disclosure teaches that a biologically active fragment is a fragment of a full-length reference polynucleotide or polypeptide which fragment retains the activity of the reference polynucleotide or polypeptide respectively (see e.g. page 23, line 22-24). A variant displays substantial sequence identity and hybridizes with the reference sequence under stringent conditions or differs from a reference by an addition, deletion or substitution of at least one nucleotide or allelic variants which retain the biological function or activity (see page 31, line 1-13). In the instant case, applicants do teach that the protein-destabilizing element is for example the d1 mutant of mouse ornithine decarboxylase, which contains a PEST sequence. However, applicants do not disclose actual sequences corresponding to PEST, N-terminal destabilizing amino acids or ubiquitin sequences. The prior art does nto teach a correlation between fragments of these sequences and their ability to provide protein degradation ability. Without disclosing the sequences, the structural requirements of the protein destabilizing elements cannot be known such that biologically active fragments, variants and derivatives of these elements could be identified. Therefore, there is no disclosure of a structure-function relationship between the sequence of PEST sequences, N-terminal destabilizing amino acids, ubiquitin elements and their protein degrading activity. Given the large size and diversity of fragments, variants and derivatives and the inability to determine which will also provide the required function, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of no species would represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

In the instant case, applicants disclose that the construct of the instant invention comprises reporter genes and selectable marker genes and these are well known in the art. There is no disclosure as to biologically active fragments, variants or derivatives of the recited genes. Furthermore, the specification does not disclose any of the sequences of the recited genes nor provide a description of the genes such that the structural requirements of the genes can be envisioned. Given the large size and diversity of the recited genes, the absence of disclosed or art recognized correlations between structure and function and the large number of potential fragments, variants and derivatives, it must be considered that any biologically active fragments, variants or derivatives of these. Applicants have not reduced to practice the claimed invention and the relationship between structure and function is unclear. In an unpredictable art, the disclosure of no examples would represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 28, 41, 44-47 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 44-47 and 49 are vague and indefinite in that the metes and bounds of the term "derivative" are unclear. It is unclear the nature and number of steps required to obtained a "derivative" of the recited molecules. The term implies a number of different steps that may or

may not result in a change in the functional characteristics of sequences from the source that it is "derived from". It would be remedial to amend the claim language to use the term "obtained from", which implies a more direct method of acquiring the various products.

Claim 41 is vague and indefinite in that the metes and bounds of "clonable directly" are unclear. It is unclear to what directly refers and what about the vector must be provided such that PCR products can be cloned directly into the vector.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23-26, 30, 33, 34, 36, 37, 39-42, 50-56, 68, 85 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Shyu et al (Genes and Development, 1989, Vol 3, pages 60-72; see entire document).

Shyu et al teach the generation of an expression vector comprising *c-fos* instability elements, ARE, which comprises SEQ ID NO:1 and SEQ ID NO:19 (see e.g. figure 1) and a second novel element within the *c-fos* protein coding region (See e.g. page 61, col 1, paragraph

2). The vector comprises the instability elements as a *c-fos*/β-globin fusion and a site into which promoters such as β-globin or c-fos promoters, which are cis-acting regulatory elements that enhance transcription, have been inserted. The half-life of the fusion protein is 28+/-2 minutes (see e.g. page 63, col 2 paragraphs 2-3). The vector originates from T7/T3-alpha 18, which comprises an f1 origin of replication as well as ampicillin selection marker and multiple cloning sites through which the vector can be linearized to insert PCR products. The stability of the construct was assayed in NIH-3T3 cells (see e.g. page 63, col 2, paragraph 2).

Claims 23-26, 30, 31, 33-37, 39-41, 46, 50-55, 58 and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by Newman et al (Plant Cell, Vol 5, pages 701-714; see entire document) as evidenced by Fang et al (Plant Cell, Vol 1, pages 141-150; see entire document).

Newman et al teach construction of a vector comprising a plant DST sequence that targets reporter transcripts for rapid decay. Reporter genes include β-glucuronidase and β-globin and CAT (see e.g. page 702, col 2, paragraph 2 and page 703, col 2, paragraph 2) which includes enzyme based reporter genes. Furthermore, the vector based upon pMON505-70 as evidenced by Fang et al comprises sites for insertion of promoters as evidenced by insertion of 35S promoter of cauliflower mosaic virus and furthermore comprises polyadenylation sequences, selectable markers and sites for insertions of gene-expressing modulating elements such as at the Cla I or Xho I or Hind III site, part of a multiple cloning site (see e.g. Fang et al, figure 1).

Claims 23-25, 30-37, 39-41, 46-48, 50-57 and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by Giordano (US 2004/0091866; see entire document) as evidenced by Promega, PGL-3 map.

Giordano et al teach methods for identifying novel nucleic acid regulatory elements and compounds that affect regulation (see e.g. abstract) using vectors comprising reporter genes such as renilla luciferase (Luc), chloramphenicol acetyltransferase (CAT) and green fluorescence protein (GFP) (see e.g. paragraph 0029), which reporter functions include enzyme based reporters and light emitting reporters. UTR sequences were inserted into cloning sites to assess for example sequences that affect the stability of the transcript such as destabilizing the transcript (see e.g. paragraph 0032). A particular vector based upon PGL3 (Promega) in which the reporter is a fusion between luciferase, a reporter gene and Her2, which functions as a selectable marker (see e.g. paragraph 0036). PGL-3 comprises a multiple cloning site, which can be linearized for insertion of a PCR product, an SV40 polyadenylation signal, an origin of replication and a selectable marker. Furthermore, the vector includes a site for insertion of a gene expressing modulating element (see e.g. figure Promega). MCF-7, human breast cancer cells are used to assay the stability of the reporter (see e.g. paragraph 0035).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-28, 30-37, 39-42, 44-48, 50-57, 68 and 85-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorens et al (US 2004/0002056; see entire document) in view of Shyu et al (Genes and Development, 1989, Vol 3, pages 60-72; see entire document) or Giordano et al (US 2004/0091866; see entire document).

Applicants claim a construct comprising a polynucleotide that encodes a polypeptide with a protein-destabilizing element and a nucleic acid sequence that encodes a RNA element that modulates the stability of the transcript and a site for insertion of a gene expression-modulating element.

Lorens et al teach use of self-inactivating vectors comprising reporter genes. The reporter gene can be Renilla or firefly luciferase (see e.g. paragraph 0243 or 0016), light emitting reporter proteins. Host cells include human cells (see e.g. paragraph 0153). The reporter gene comprises either PEST sequences or destruction boxes such that the reporter can more adequately serve as an indicator of real time events such as transcriptional activity (see e.g. paragraph 0020, 0130 and 0243). The vector comprises polyadenylation sequences as well as insertion sites for gene expressing modulators as evidenced by insertion of heterologosu promoters such as E_{μ} and 3' α E (see e.g. figure 4). The vector is used in methods of assaying the effect of agents on gene expressing activity (see e.g. 0013).

Lorens et al do not teach inclusion of an RNA destabilizing element in the vector.

The teachings of Shyu et al or Giordano et al are described above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add to the vector of Lorens et al the RNA destabilizing element taught by Shyu et al and Giordano et al because Lorens et al teach that it is within the ordinary skill of the art to

generate a vector comprising a reporter gene with an protein degradation element for analysis of real time gene expression in cells and because Shyu et al and Giordano et al teach that it is within the ordinary skill of the art to include a RNA destabilizing element in a vector. One would have been motivated to do so in order to receive the expected benefit of decreased stability of the reporter mRNA to provide an indicator if dynamic cellular processes such as transcriptional activity (see Lorens et al, paragraph 0130) by insertion of i.e. the c-fos AU rich element which results in rapid decay of the mRNA (see e.g. Shyu et al , page 61, col 1, paragraph 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shyu et al (Genes and Development, 1989, Vol 3, pages 60-72; see entire document) or Giordano et al (US 2004/0091866; see entire document) or Lorens et al (US 2004/0002056; see entire document) in view of Primig et al (Gene, 1998, Vol 215, pages 181-189; see entire document).

Applicants claim a construct comprising a chimeric gene comprising a coding sequence from a gene encoding a light emitting protein and a selectable marker protein and a nucleic acid sequence that encodes a RNA element that modulates the stability of a transcript encoded by the chimeric gene.

The teachings of Shyu et al or Giordano et al or Lorens et al are described above and are applied as before except:

Neither Shyu et al nor Giordano et al nor Lorens et al teach that the reporter is a chimeric gene encoding comprising genes encoding light emitting protein and a selectable marker protein.

Primig et al teach use of a reporter gene that is a fusion between GFP and neomycin phosphotransferase (see e.g. page 183, bridging paragraph col 1-2). Gene expression modulating sequences were cloned into the vector and expression driven by the sequences was assayed (see e.g. (page 186, bridging paragraph col 1-2). The benefits of the vector were localization of reporter and selection functions in one gene decreasing chances of undesirable recombination events, reducing false positives, optimal conditions for identifying gene expression modulators (see e.g. bridging paragraph page 187-188).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the separate reporter and selectable marker genes taught by Shyu et al and Giordano et al or Lorens et al with the GFP-neo fusion taught by Primig et al because Shyu et al and Giordano et al and Lorens et al teach that it is within the ordinary skill of the art to generate a vector comprising a reporter gene for analysis of gene expression in cells and because Primig et al teach that it is within the ordinary skill of the art to use GFP-neo as a reporter gene in cells. One would have been motivated to do so in order to receive the expected benefit of localization of reporter and selection function sin one gene decreasing chances of undesirable recombination events, reducing false positives, optimal conditions for identifying gene expression modulators (see Primig et al, bridging paragraph page 187-188). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shyu et al (Genes and Development, 1989, Vol 3, pages 60-72; see entire document) or Giordano et al (US 2004/0091866; see entire document) or Lorens et al (US 2004/0002056; see entire document) in view of Svensson and Akusjarvi (EMBO J. 1985, Vol 4, No. 4, pages 957-964; see entire document).

Applicants claim a construct comprising a polynucleotide and a nucleic acid that encodes an RNA element that modulates stability of a transcript and a site for introducing a gene expression-modulating element and a translational enhancer.

The teachings of Shyu et al or Giordano et al or Lorens et al are described above and are applied as before except:

Neither Shyu et al nor Giordano et al nor Lorens et al teach that the vector further comprises a translational enhancer.

Svensson and Akusjarvi teach the use of adenovirus VA RNAI on the translation of mRNAs. The expression was elevated 2-6 fold (see e.g. abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add to the vector of Shyu et al or Giordano et al or Lorens et al the VA RNAI translation enhancer taught by Svensson and Akusjarvi because Shyu et al or Giordano et al or Lorens et al teach that it is within the ordinary skill of the art to generate a vector comprising a reporter gene with for analysis of gene expression in cells and because Svensson and Akusjarvi teach that it is within the ordinary skill of the art to include a translational enhancer in a vector. One would have been motivated to do so in order to receive the expected benefit of enhanced reporter activity to identify low signaling events or elements that modulate these events. Based

upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER

December 3, 2004